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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,618	HENNING ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2 and 6-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3-5 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/02, 2/19/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed April 5, 2005 in response to the Office Action of November 8, 2004 is acknowledged and has been entered. Claims 1-11 are pending in the application. Claims 2 and 6-8 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 3-5 and 9-11 are currently under prosecution.

2. The response to the restriction requirement of November 8, 2004 has been received. Applicant has elected Group A, claims 1-3 and 9-11, directed to two polypeptide markers and the species wherein the markers are selected from at least one of her2/neu and p53 for further prosecution. Claim 4 will be examined as it is drawn to the combination of the elected species, that is her2/neu and p53.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a). Upon review and reconsideration and in view of the art, claim 5 has been rejoined to the examined group. It is noted that upon review of the claims it was found that claim 2 is drawn to gene molecular markers rather than polypeptide molecular markers and thus it is clear that claim 2 was not meant to be included in the claims of Group 1. In a telephone interview with Susan M. Pellegrino on June 14, 2005, Examiner offered to send out a new restriction requirement, indicating that claim 2 is not part of the Group 1. Ms. Pellegrino reviewed the claims with Examiner and agreed that claim 2 was not drawn to polypeptides and agreed that the group to be examined is drawn only to polypeptides and that it is appropriate to withdrawn the claim from examination at this time as not being drawn to an elected invention.

Claim Objections

3. Claim 4 is objected to because it appears that Applicant has made an inadvertent typographical error in the claim. The claim is drawn to a method "characterized in that the marker combinations her2/neu with p16.....". It appears that the claim was meant to recite "characterized in that the marker combinations are selected from the group including". Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-5 and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-5 and 9-11 are indefinite because claim 1 does not contain a positive process step which clearly relates back to the preamble.

Claims 1, 5 and 9-11 are indefinite because claim 1 recites the limitations of "at least two molecular markers" in a cell. The claims are indefinite because they appear to be missing a critical element, such omission amounting to a gap between the elements. See MPEP 2172.01. That is, the element of detecting at least two molecular markers, that have been observed in connection with tumor cells. Although the specification states that the expression "molecular marker" comprises molecular changes in cells, in particular changes in gene expression which have

been observed in connection with a cell constitution which is altered or is pathological", it is noted that given the "comprising" language, the definition is not limiting.

Claims 9-10 are indefinite because claim 9 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the application of the combined and summated signal intensities to the detection of the tumor cells or their precursors.

Claims 9 and 10 are indefinite because claim 9 recites the phrase "signal intensities are combined and summated". The claim is confusing because it is not clear which signal intensities are intended to be combined and summated. Is it the intensities of all signals whether specific or non-specific? Is it the intensities of those cells that contain only a single marker? A double marker? All three markers? Given the above, the metes and bounds of the claims cannot be determined.

Claim 10 is indefinite in the recitation of "the automatic information processing". There is no antecedent basis for the phrase in claim 9 from which claim 10 depends.

Claim 10 is indefinite in the recitation of "where appropriate". The claim is indefinite because the term "appropriate" is a relative term. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103 that form the basis for the rejections under this section made in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the

differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 and 3, 5, 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pillai et al (Cancer Epidemiology, Biomarkers and Prevention, 1996, 5:329-335, IDS item) in view of US 20020045591.

The claims are drawn to a method for detecting tumour cells and their precursors in uterine cervical smears by simultaneously detecting at least two polypeptide molecular markers in a cell (claim 1), wherein at least one of the markers is present in the combination is p53 or bcl-2 polypeptide (claim 3) at least three polypeptide markers (claim 5), wherein abnormal cells are detected in an automated manner, wherein at least two markers are detected, wherein the method comprises at least two of fully automatic sample reading and information processing (claim 11).

Pillai et al teach a method for detecting tumor cells and their precursors in cervical smears, an assay for the presence of multiple markers for cervical cancer and teach immunoflorescence assay for Bcl-2 using tetramethylrhodamine isothyocyanate antihamster antibodies or p53 in cervical smears using anti-mouse FITC conjugated antibodies (p. 330, col 1) as well as assay for HPV expression (p. 330, col 2). The cells were imaged using an epifluorescence microscope coupled to a low level camera and a digital image analysis system (p. 330, col 2), wherein it is clear that the digital image analysis system automatically reads the sample and processes information drawn to that sample. No HPV-16 E6 staining and little bcl-2 staining was observed in normal cells and p53 staining was found predominantly in the nucleus. When present in smears from patients with cervical disease, p53, bcl-2 and E6 staining was found in cytoplasm (para bridging pages 331-332). A review of Table 1 reveals that ten percent of the smears from Cin I patients presented with three markers, p53, bcl-1 and E6. It would be expected that at least a subset of these smears would present with a cell comprising cytoplasmic p53, bcl-2 and E6, which clearly identifies a precursor of a tumor cell. Further, Table 1 discloses that eleven percent of the smears from invasive cancer patients presented

with three markers, p53, bcl-1 and E6. It would be expected that at least a subset of these smears would present with a cell comprising cytoplasmic p53, bcl-2 and E6 which clearly identifies a tumor cell in the uterine cervical smear from a cervical cancer patient.

Pallai et al teach as set forth above, but does not appear to simultaneously assay for p53, Bcl-2 and E6.

US 20020045591 specifically teaches the conventional use of triple immunofluorescence microscopy (see para 0141 of the Detailed Description).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the methods of Pallai et al and US 20020045591 in order to simultaneously immunoassay for bcl-2, p53 and E6 in the smear samples of Pallai et al with conventional triple immunofluorescence microscopy because the conventional triple immunofluorescence microscopy would save time, labor and reagents in the assay process. One would have been motivated to have combined the methods of Pallai et al and US 20020045591 in order to simultaneously immunoassay for bcl-2, p53 and E6 in the smear samples of Pallai et al with conventional triple immunofluorescence microscopy in order to reduce overall costs and to deal with the limited sample volumes presented by the use of smear samples.

8. Claim 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pallai et al, *Supra* US 20020045591 and further in view of Kihana et al (Cancer, 1994, 73 :148-153).

The claims are drawn to a method for detecting tumour cells and their precursors in uterine cervical smears by simultaneously detecting at least two molecular markers in a cell (claim 1), wherein at least one of the markers in the

combination is p53, is her2/neu (claim 3), wherein the combination is p53 with her2/neu (claim 4), wherein three markers are detected (claim 5).

Pallai et al and US 20020045591 teach as set forth above but do not teach assay of her2/neu, also known as C-erbB-2, as one of the multiple markers for cervical cancer or the combination of C-erbB-2 with p53.

Kihana et al teach the immunoassay of formalin-fixed paraffin-embedded tissue sections of cervical adenocarcinoma for C-erbB-2 protein which was detected in 77% (34 of 44 cases) of the tumor tissues assayed (see abstract and p. 149, col 1) but only in 13% (1 of 8) of the non-tumor samples tested. Thus it appears that given the expression of C-erbB-2, it is more likely than not that a sample would be positive for cervical cancer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the assay of the c-erbB-2 of Kihana et al for either bcl-2 or E6 in the method of Pallai et al because Kihana et al teach that C-erbB-2 is expressed in the vast majority of cervical carcinoma samples tested. One would have been motivated to include the C-erbB-2 of Kihana et al in the multiple marker assay for cervical cancer in order to detect an additional marker that would give additional information that would be useful in determining the therapeutic approach to the treatment of the patient, since herceptin treatment of cancers expressing C-erbB-2 is well known in the art. One would have had a reasonable expectation of successfully identifying C-erbB-2 in the method of Pallai et al because Kihana teach that 77% of the samples assayed expressed the C-erbB-2 protein and given the expression of the marker in the majority of cervical carcinoma samples, it is reasonable to expect that the marker would also be present in Pap smear cells as well. Finally, one would expect that at least a subset of the

cells of samples from advanced carcinoma patients tested would express at least C-erbB-2 and p53, given the overlap of patients expressing both markers wherein Pallai et al teach that 25% of patients with invasive cancer of the cervix present with p53 (p. 332, Table 1) and the teaching of Kihana et al that 77% of the patients with adenocarcinoma present with C-erbB2. Given the expression overlap, one would have a reasonable expectation of detecting tumor cells by simultaneously detecting p53 and C-erbB2. Although neither reference specifically teaches that C-erbB2 is expressed in cervical smear cells, the claimed method appears to be the same as the method of the combined references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art combined references and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

9. Claims 1 and 9-10 are rejected under 35 U.S.C. § 103 as being anticipated by Pillai et al, *Supra* in view of US 20020045591 and further in view of Levenson et al, ISAC XX Purdue Cytometry CD ROM Series, May, 2000, Vol 5, Abstract Number 8047 and Stoler (Advances in Cervical Screening Technology, Mod. Pathol., 2000, 13:275-284, IDS item).

It is noted that due to the indefinite nature of the claims it is assumed for examination purposes that the "signal intensities" that are combined and summated

are those that are drawn to the overlapped intensities expected to be found in a single cell that presents with all three of the markers of the combined references.

The claims are drawn to a method for detecting tumour cells and their precursors in uterine cervical smears by simultaneously detecting at least two polypeptide molecular markers in a cell (claim 1), wherein the method enables abnormal cells to be detected in an automated manner, characterized in that at least two markers are detected and the signal intensities are combined and summated (claim 9) wherein the automatic information processing is combined with a diagnostic expert system which enables the image information to be consolidated into a proposed diagnosis (claim 10).

Pillai et al in view of US20020045591 teach as set forth above but do not teach the combination of signal intensities and the summation of those intensities, do not teach the automatic information processing combined with a diagnostic expert system which enables the image information to be consolidated into a proposed diagnosis.

Levenson et al teach that PAP-stained pathology sections evidence a rich spectral behavior which can be used to separate normal from neoplastic cells using spectral "signatures" and simple segmentation algorithms. Spectral imaging can also be used to quantitatively detect the presence of at least three immunohistochemical chromogens, even if they overlap spatially (see Results Section of the abstract).

Stoler et al teach that for the past year, the AutoPap system has been the only device approved for primary screening of Pap smears. The AutoPap system allows up to 25% of the most normal slides that are scanned into the system to be sorted out for no further human review (p. 279, col 1), thus consolidating a

proposed diagnosis of no pathology for those slides and consolidating a proposed diagnosis of pathology in the slides that are not sorted out.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined and summated the signal intensities of overlapping signals from cells which present with at least two of the three markers of the combined references of Pallai et al and US20020045591 because Levenson et al teach that spectral imaging can be used to quantitatively detect the presence of three immunohistochemical chromogens, even if they overlap spatially. Thus, using this technique one could quickly and efficiently identify those cells that comprise at least two of the three markers as well as quickly and efficiently determine the number of cells that comprise at least two of the three markers. One would have been motivated to summate and combine the signal in order to determine the concentration of precursor or malignant cells in the sample and thus be able to determine the extent of malignant or precursor cells. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the use the AutoPap system of Stoler with the method of the combined references because Stoler specifically teaches that the AutoPap system allows up to 25% of the most normal slides that are scanned into the system to be sorted out for no further human review thus consolidating a proposed diagnosis of no pathology for those slides and consolidating a proposed diagnosis of pathology in the slides that are not sorted out. One would have been motivated to include the AutoPap analysis in the method of the combined references in order to save both time and money in the analysis of the pap smears for cervical cancer screening.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar
Primary Patent Examiner
June 20, 2005